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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/669,823	SUN ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-133* is/are pending in the application.

4a) Of the above claim(s) *20-95,97-100,102-105,107-110 and 114-125* is/are withdrawn from consideration.

5)☒ Claim(s) *1-19,96 and 111-113* is/are allowed.

6)☒ Claim(s) *101,106 and 130-133* is/are rejected.

7)☒ Claim(s) *126-129* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response field on 1/27/2006, is made of record. Claims 1-133 are pending. Claims 20-95, 97-100, 102-105, 107-110 and 114-125 were withdrawn from consideration in the previous office action. Claims 1-19, 96, 101, 106, 111-129 and 130-133 are under examination.

In view of applicants' response, the following rejection made in the previous office action is maintained. Applicants' pointing out an error in the list allowed claims is gratefully acknowledged.

Information Disclosure Statement

References cited in the Information Disclosure Statement , filed on 1/27/2006, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 101, 106 and 130-133 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain due to headache or arthritis, does not reasonably provide enablement for treating any or all pain originating from various diseases generically embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for reasons of record. To repeat: Following reasons apply.

First of all, instant claims are reach through claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification.

In the instant case, it appears that, because the instant compounds interact with vanilloid receptor and that vanilloid receptors are present in the human body, it is recited that any or all pain can be treated with the instant compounds for which there is no adequate written description and enabling disclosure. Furthermore, references provided in the Information Disclosure Statement either alone or in combination do not provide support for the scope of generically embraced in the instant claims.

The scope of the claims includes treating any or all pain arising from various diseases and disorders as mediated by vanilloid receptor for which there is no enabling disclosure. More specifically the scope of these claims includes treating pain associated with an inflammatory disease such as organ transplant rejection; reoxygenation injury resulting from organ transplantation , transplantation of the heart, lung, liver, or kidney', cllronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resoption; inflammatory bowel diseases, such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory disease of the gum,

including gingivitis and periodontitis; tuberculosis; leprosy; inthmmatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory disease of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer 's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis', autoimmune diseases, including Type I and Type 11 diabetes mellitus', diabetic complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy (such as microaluminuria and progressive diabetic nephropathy), polyneuropathy, mononeuropathies, autonomic neuropathy, gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin spot, a Candida infection or necrobiosis lipoidica diabeticoruml; immune-complex vasculitis, and systemic lupus erythematosus (SLE), inflammatory disease of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and atherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer and many others., which are not adequately enabled solely based on the inhibiting vanilloid receptor activity of the compounds provided in the specification at pages 1-8 and 147-150. The instant compounds are disclosed to have inhibiting vanilloid receptor activity

and it is recited that the instant compounds are therefore useful in treating any or all diseases where vanilloid receptor activity is implicated, for which applicants provide no competent evidence. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. The scope of the claims involves all of the thousands of compounds of instant claims as well as the thousand of diseases embraced by the terms inflammatory diseases, non-vascular syndromes etc

Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. There is a vast range of forms that it can take,' causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are hundreds such diseases, which have fundamentally different mechanisms and different underlying causes. Thus, the scope of claims is extremely broad.

Furthermore, , treatment of individual disease/disorder need not extrapolate to treating any or all generic diseases.

For example, although there are compounds for treating headache, they are not found to treat any or all pain such pain suffered by cancer patients.

No compound has ever been found to treat all types of pain. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Dogurl et al., Di Marzo et al., and Foley cited in the Information Disclosure Statement which indicative of further future experimentation. See also Valenzano et al. Curr. Med. Chem. 3185-3202, 2004 (PubMed Abstract provided), and Szallasi et al, Journal of Medicinal Chemistry 47(20): 2716-2723, 2004.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence

or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating any or all pain from various diseases and disorders that require inhibiting vanilloid receptor activity.

2) The state of the prior art: Recent publications expressed that treating disease or disorders by the inhibition of vanilloid receptor is still exploratory. See Valenzano et al., as well as Szallasi et al. cited above. Note all these references state the vanilloid receptor-mediated diseases/disorders in general are at best in the early experimental stage and needs further exploratory studies.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all pain arising from any or all diseases or disorders of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all pain and the state of the art is that the effects of inhibiting vanilloid receptor activity are unpredictable and at best limited to modulation of rheumatoid arthritis.

6) The breadth of the claims: The instant claims embrace any or all diseases and disorders related vanilloid receptor.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

This rejection is same as made in the previous office action. Applicants' traversal is not persuasive. Following apply.

First of all, as noted in the above rejection, the rejection is based on Wands factor analysis.

Secondly, as noted above, the instant claims are reach through claims. based on the mode of action of the instant compound namely interaction with VR1 receptor , it is claimed that any or all pain can be treated. Hence, contrary to applicants' urging, the issue is not whether instant compounds have said interaction or not . therefore thte fact tht instant compounds have favorable IC50 is not issue but whether such interaction would permit treading all or any pain and whether specification has disclosure for the scope embraced.

Thirdly, the enablement of arthritis pain or headache is not deemed as objective enablement for treating cancer pain or neuropathic pain etc. For example, commonly used aspirin or tylenol is not effective for treating cancer pain and it is evident from the debate about legal issue of cannabinoids for cancer pain.

As agreed by the applicants, 112 first paragraph requires objective enablement and that is what lacking. Applicants have not shown that treating one disease would be an objective enablement for any or all diseases. In fact modern medicine does not lend support for such a notion. For example treating hypertension would not provide objective enablement for lupus or cancer or bacterial infection. As for applicants reliance on In re Marzocchi, 439 F.2d 220,169 USPQ 367(CCPA 1971), it relates to objective enablement. Instant specification has no objective enablement treating any or all pain mediated by VR1. Hence, In re Marzocchi, is not to the point.

Relevant passages of In re Marzocchi is presented below for applicants' careful review:

Court states: "Recitation of generic term "polyethyleneamine" must be taken as assertion by applicants that all of the "considerable number of compounds" which are included within generic term would, as a class, be operative to produce asserted enhancement of adhesion characteristics; Patent Office has no concern over breadth of term; its only relevant concern should be over truth of such assertion; first paragraph of 35 U.S.C. 112 requires nothing more than objective enablement; how such a teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance. "

So according to court, the breadth of the term "polyethyleneamine should not be issue. This is not the case with instant compounds. Court clearly asserts requirement for objective enablement.

Court adds further: "Turning specifically to the objections noted by the board as indicated above, it appears that these comments indicate nothing more than a concern over the breadth of the disputed term. Accepting, therefore, that the term is a generic one, its recitation must be taken as an assertion by appellants that all of the "considerable number of compounds" which are included within the generic term would, as a class, be operative to produce the asserted enhancement of adhesion characteristics.

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.

In the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, 4 will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the

applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. Cf. In re Gazave, 54 CCPA 1524, 379 F.2d 973, 154 USPQ 92 (1967); In re Chilowsky, 43 CCPA 775, 229 F.2d 457, 108 USPQ 321 (1956)."

In the present case, specification has no objective enablement for any or all pain mediated by VR1. Contrary to applicants urging, with the genus of compounds and large list of diseases, one trained in the art had to extensively undue experimentation.

Fourthly, the model shown in the references did not suggest or teach that any or all pain cannot be treated with the model. The fact that two different model were studied is indicative of the variation in the response to pain. See Seltzer model and Chung model.

Fifthly, applicants allegation that examiner had made personal comments lacks factual basis. Applicants are urged to point out where such remarks are made. The factual basis for stating the treating arthritis pain and headache emerges from the prior art and what is known. Examiner can point out what is not enabled. In the instant based specication recites "treating pain associated with an inflammatory disease such as organ transplant rejection; reoxygenation injury resulting from organ transplantation , transplantation of the heart, lung, liver, or kidney', cllronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resoption; inflammatory bowel diseases, such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal dystrophy, trachoma,

onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory disease of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inthmmatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory disease of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer 's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis', autoimmune diseases, including Type I and Type 11 diabetes mellitus', diabetic complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy (such as microaluminuria and progressive diabetic nephropathy), polyneuropathy, mononeuropathies, autonomic neuropathy, gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin spot, a Candida infection or necrobiosis lipoidica diabeticoruml; immune-complex vasculitis, and systemic lupus erythematosus (SLE), inflammatory disease of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and atherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer and many others" and there is no disclosure enabling the scope embraced.

Applicants have argued that inflammation caused by various mechanism is irrelevant to whether the method of treatment caused by a condition is enabled. But instant claims rely on the mode of action of the VR1 as basis for treating pain in general and it is not clear why the mode of action is relevant if the mechanisms causing the pain is irrelevant.

Contrary to applicants' urging, the fact that later dated references cited by the examiner, do not lend support for treating any or all pain and indicative of further experimentation , is equally applicable earlier date of the invention. It stands reasoning that if the such a treatment is unpredictable presently then it would also be true at the time of invention which ahs earlier date. One trained in the art need to extensive undue experimentation with large genus of compounds and huge list of diseases to find which pain can be treatable. As for In re Borkowski, 411 F.2d 904, 164 U.S.P.Q 642, 645 (C. C.PA 1970), it is clearly that extensive undue experimentation is needed to arrive at which pain is treatable and it s not a routine experimentation given the variation in testing among different models.

Hence, this rejection is deemed as proper and is maintained.

Allowable Subject Matter

Claims 1-19, 96 and 111-113, barring finding of any prior art in a subsequent search, and deletion of any non-elected subject matter, would be allowed.

Applicants should note the error in indicating claims 111-129 as allowable has been corrected by replacing 111-129 with 111-113.

Claims 126-129 are objected to as containing non-elected subject matter but would be allowable if rewritten to embrace elected subject matter.

Election/Restrictions

This application contains claims 20-95, 97-100, 102-105, 107-110 and 114-125 drawn to an invention nonelected with traverse in Paper dated 9/23/2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. See claim 126-129 as well.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is

James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

4/16/2006